Evaluation of Nickel Release from Endobronchial Valves as a Possible Cause of Hypersensitivity Pneumonitis in a Patient Treated with Bronchoscopic Lung Volume Reduction

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Abstract: BACKGROUND:Endobronchial valve (EBV) placement is an established lung volume reduction procedure aiming to improve lung function and exercise capacity in patients with severe emphysema. As EBVs consist of silicone and nitinol (a metal alloy of nickel and titanium), there are concerns that nickel ions might be released and could have a clinical impact in patients with a contact allergy to nickel. Based on a case with hypersensitivity pneumonitis (HP) after treatment with EBVs, we aimed to evaluate the in vitro nickel release from EBVs using inductively coupled plasma mass spectrometry (ICP-MS) and scanning electron microscopy (SEM). METHODS:Six EBVs were immersed in artificial saliva for a period of 7 days. At 24-h intervals, the nickel ion concentration was measured using ICP-MS. RESULTS:There was evidence of a significant nickel release from EBV during the first 48 h, which is possibly due to an incomplete silicone layer detected by SEM. The concentration of released nickel was below the toxic limit. CONCLUSIONS:To the best of our knowledge, we report the first case of HP after EBV treatment. Our finding of in vitro release of nickel ions from EBVs may contribute to the current understanding on hypersensitivity reactions after nitinol implants in patients with nickel contact allergy. However, it did not confirm a causative relationship.

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Keywords
Bronchoscopic lung volume reduction · Endobronchial valves · Nickel contact allergy · Nickel release · Hypersensitivity pneumonitis

Abstract
Background: Endobronchial valve (EBV) placement is an established lung volume reduction procedure aiming to improve lung function and exercise capacity in patients with severe emphysema. As EBVs consist of silicone and nitinol (a metal alloy of nickel and titanium), there are concerns that nickel ions might be released and could have a clinical impact in patients with a contact allergy to nickel. Based on a case with hypersensitivity pneumonitis (HP) after treatment with EBVs, we aimed to evaluate the in vitro nickel release from EBVs using inductively coupled plasma mass spectrometry (ICP-MS) and scanning electron microscopy (SEM). ***Methods:*** Six EBVs were immersed in artificial saliva for a period of 7 days. At 24-h intervals, the nickel ion concentration was measured using ICP-MS. ***Results:*** There was evidence of a significant nickel release from EBV during the first 48 h, which is possibly due to an incomplete silicone layer detected by SEM. The concentration of released nickel was below the toxic limit. ***Conclusions:*** To the best of our knowledge, we report the first case of HP after EBV treatment. Our finding of in vitro release of nickel ions from EBVs may contribute to the current understanding on hypersensitivity reactions after nitinol implants in patients with nickel contact allergy. However, it did not confirm a causative relationship.

Introduction

Bronchoscopic lung volume reduction (BLVR) with endobronchial valves (EBVs) has been shown to improve pulmonary function and exercise capacity in patients with severe emphysema [1–3]. EBVs are 1-way valves which are implanted bronchoscopically into the segmental bronchi, disabling airflow to a target region of the diseased lung, and allowing trapped air to escape. Eventually, the lung volume reduction effect is achieved by lobar atelectasis to reduce hyperinflation [4]. There are 2 types of EBV, both consisting of a frame made of nitinol, a metal alloy of nickel and titanium, which is covered by a silicone membrane. Due to its unique combination of shape memory, elasticity properties, and biocompatibility response, nitinol is widely used in medicine for orthodontic arch wires, filters, stents, bone anchors, and EBVs [5].

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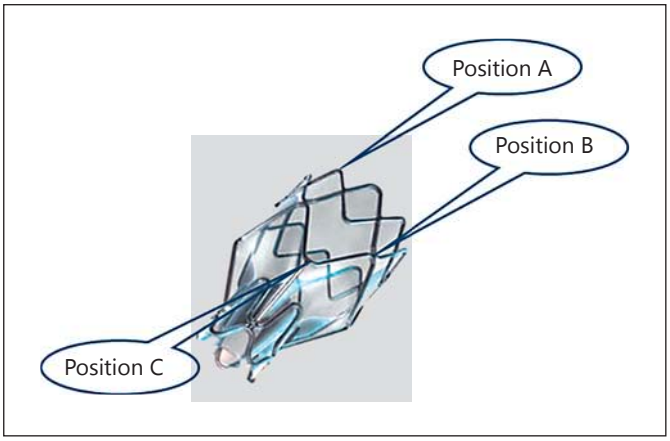

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Fig. 1. An endobronchial valve (Pulmonx Sarl, Neuchâtel, Switzerland) showing the positioning of the scanning electron microscopy images.

Formally, EBVs are contraindicated in patients with known allergies to nitinol or silicone [6]. In addition, there is controversy regarding the effects of nickel alloy-based device implantation in patients with nickel contact allergy, since there is concern about the release of nickel after nitinol device implantation [7, 8].

To the best of our knowledge, a case of hypersensitivity pneumonitis (HP) after treatment with EBVs in a patient with nickel allergy has not yet been reported. Based on this case, we aimed to evaluate the in vitro nickel release from EBVs using inductively coupled plasma mass spectrometry (ICP-MS) and scanning electron microscopy (SEM).

Methods

Two new (2 × 4.0 mm) and 4 used EBVs (2 × 4.0mm and 2 × 5.5 mm, Zephyr®, PulmonX International Sàrl, Neuchâtel, Switzerland) were evaluated with SEM and ICP-MS. The used EBVs had been explanted from another patient due to collateral ventilation after an inbody period of 2 months. All measurements were performed at The Laboratory of Central Switzerland, Brunnen (Lab 1) and The Zurich University of Applied Sciences, Wädenswil (Lab 2), Switzerland.

Inductively Coupled Plasma Mass Spectrometry

All 6 EBVs were immersed and shaken (shaking frequency 100 times/min) in 3 mL of artificial saliva (Glandosane®, Helvepharm AG, Frauenfeld, Switzerland) at 37°C for a period of 7 days in Lab 1. One gram of Glandosane consists of: Kalii chloridum 1.2 mg, Natrii chloridum 844 µg, Magnesii chloridum 52 µg, Calcii chloridum 146 µg, Dikalii phosphas anhydricus 342 µg, Carboxymethylcellulosum natricum 10 mg, and Sorbitolum 30 mg. At 24-h intervals, 2 mL of the solution was extracted and 1:1 replaced by fresh Glandosane. The nickel content of the extracted test solution was measured using the ELAN® DRC-e ICP-MS (Perkin-Elmer, Waltham, MA, USA) with a cross-flow nebulizer.

Scanning Electron Microscopy

SEM images of EBV surfaces were captured using a Quanta FEG 250 microscope (FEI, Hillsboro, OR, USA) with a low vacuum (1.5-mbar) and without conductive coating before and after immersion in artificial saliva at the positions indicated in Figure 1. SEM imaging was performed in 2 independent laboratories to exclude handling failure. For this, a second set of 1 explanted (4.0 mm) and 1 new valve (4.0 mm) was analyzed in Lab 2 (SEM only).

Results

Clinical Case Report

A 53-year-old previous smoker (40 pack-years) with severe emphysema was referred for evaluation of BLVR, as his dyspnea and exercise capacity had worsened over the last months. Once a year, he suffered from acute exacerbations of chronic obstructive pulmonary disease (AECOPD), with the last episode being a year ago. His baseline pulmonary function test values are displayed in Table 1. Chest computed tomography (CCT; Fig. 2a, b) and lung perfusion scintigraphy revealed homogeneous emphysema with impaired perfusion of both upper zones. His medical history was otherwise uneventful, except for acute intermittent porphyria and an allergy to nickel. The latter had been confirmed by a patch test some years earlier. His medication comprised inhalational tiotropium and formoterol/budenoside, and long-term oxygen therapy (1–2 L/min). He had completed an ambulatory pulmonary rehabilitation program, but there was no distinct benefit concerning his symptoms. Since the patient declined surgical lung volume reduction, a decision was made to perform BLVR with EBVs for bridging to lung transplantation. Due to his nickel allergy, EBVs were preferred to coils, since the latter are not covered by a silicone layer, allowing nitinol to be in direct contact with the bronchial mucosa. After exclusion of collateral ventilation with the Chartis® technology (PulmonX International Sàrl) [9], 4 EBVs (Zephyr) were implanted bronchoscopically in the right upper lobe (4.0-mm valves in segments B3a and B3b, and 5.5-mm valves in segments B1 and B2). The postinterventional course was uneventful, and the patient was discharged on the third day after implantation. A month later, he reported worsening cough, increasing dyspnea, and a new itching exanthema on his trunk and face. There was no change in concurrent medication. Since AECOPD was suspected, a course of

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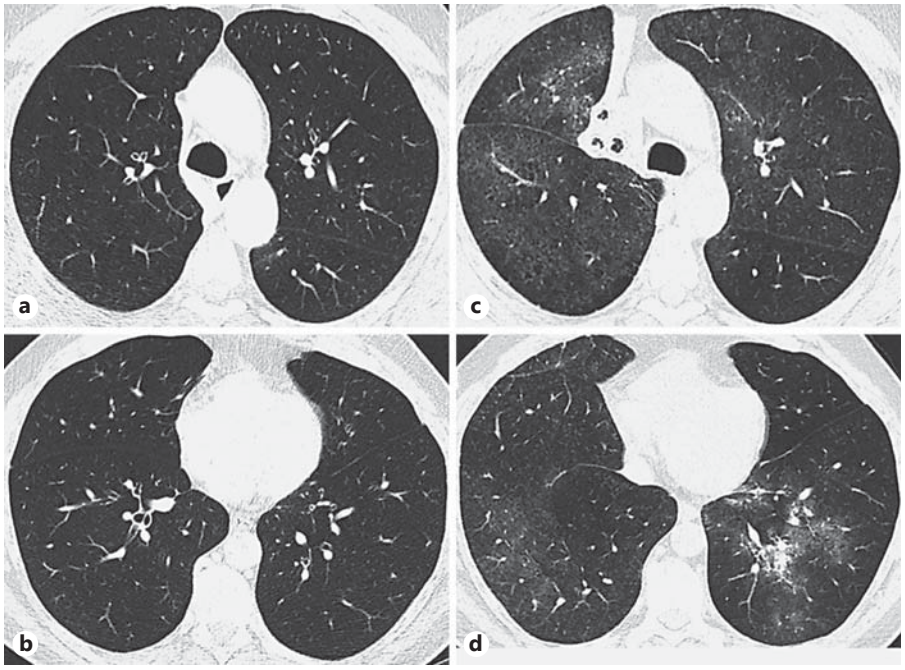

Fig. 2. Chest computed tomography (CT) before and 1 month after bronchoscopic lung volume reduction with endobronchial valves (EBVs). **a**, **b** Transverse chest CT images of the upper and lower zone (lung window) showing centroacinar pulmonary emphysema, but otherwise unremarkable lung parenchyma (no signs of interstitial lung disease, or ground-glass opacities) before EBV treatment. **c**, **d** Corresponding CT images revealing atelectasis of the right upper lobe after treatment with EBV. In addition, ground-glass opacification in the bilateral upper and lower lobes, turning into consolidation in the left lower lobe.

Table 1. Pulmonary function test values before and after bronchoscopic lung volume reduction with endobronchial valves in the right upper lobe

	Baseline	FU at 1 month	FU at 3 months (50 mg PDN)	FU at 4 months (20 mg PDN)	FU at 6 months (12.5 mg PDN)
FVC, L	2.43 (60)	2.33 (55)	2.61 (65)	3.18 (79)	2.52 (62)
FEV1, L	1.08 (33)	1.24 (37)	1.23 (38)	1.22 (37)	1.15 (35)
TLC, L	6.97 (107)	6.84 (101)	n.a.	n.a.	6.93 (107)
RV, L	5.01 (229)	4.49 (202)	n.a.	n.a.	3.75 (172)
RV/TLC, %	72	66	n.a.	n.a.	54
DLCO, mmol/min/kPA	4.86 (52)	4.05 (42)	4.53 (49)	5.32 (57)	6.57 (71)
6-MWT, m	356	n.a.	n.a.	n.a.	330
MRC dyspnea scale	4	5	3	3	3
Cough	+	+++	++	++	+

Percentage predicted values appear in parentheses. DLCO, carbon monoxide diffusing capacity of the lung; FEV_1, forced expiratory volume in 1 s; FU, follow-up; FVC, forced vital capacity; MRC, Medical Research Council; 6-MWT, 6-min walking test; PDN, prednisolone; TLC, total lung capacity, RV, residual volume; n.a., not available.

prednisolone (20 mg/day over 7 days) was given, resulting in temporary improvement of these symptoms, but they returned 2 weeks later, this time with a new onset of fever (up to 39.0°C) and chills. Laboratory parameters revealed normal counts of leukocytes, neutrophils, monocytes, lymphocytes, and eosinophils, increased C-reactive protein (97 mg/L), and normal procalcitonin (0.05 μg/L). Pulmonary function testing (Table 1) was notable for the decline of the diffusion capacity of the lung for carbon monoxide (DLCO), although the FEV_1 had improved by 160 mL, and residual volume was reduced by 480 mL. CCT (Fig. 2c, d) was performed, revealing complete right upper-lobe atelectasis after the EBV treatment, but there was marked ground-glass opacification of all other lobes with the beginning of consolidation in the left lower lobe. After bronchoscopy including bronchoalveolar lavage

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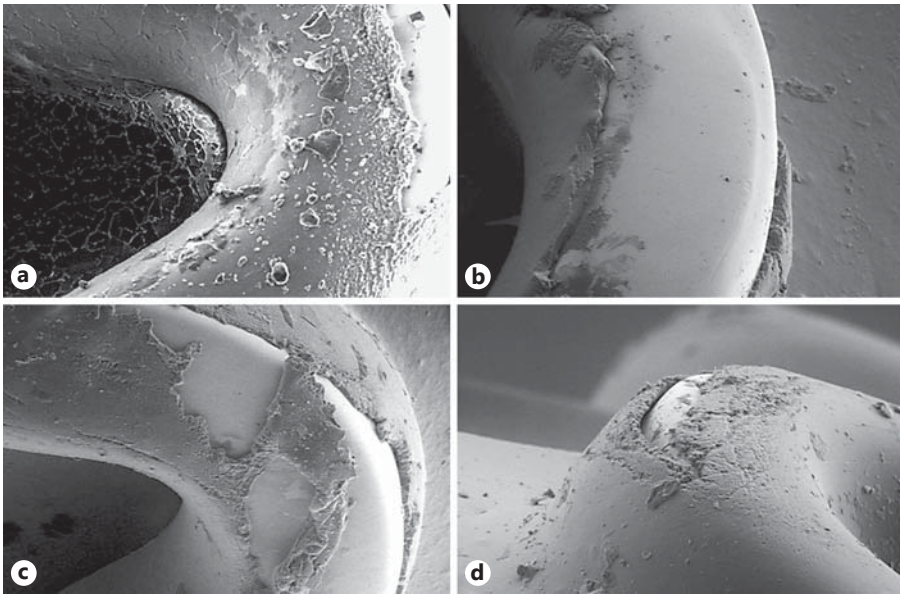

Fig. 3. Scanning electron microscopy images of the endobronchial valves (EBVs). All pictures were captured at position A in Figure 1. **a** A new EBV before immersion in artificial saliva. **b** A new EBV after immersion in artificial saliva. **c** An explanted EBV before immersion. **d** An explanted EBV after immersion. ×1,000.

Table 2. Nickel content in artificial saliva (Glandosane) after immersion of the endobronchial valves

	Total nickel release, μg/L		
	day 1	day 2	days 3–7
New EBVs			
1 (4.0 mm)	3.7	0.6	*
2 (4.0 mm)	7.5	1.4	*
Explanted EBVs			
1 (4.0 mm)	11.9	0.7	*
2 (4.0 mm)	21.5	3.2	*
3 (5.5 mm)	9.6	1.4	*
4 (5.5 mm)	16.9	2.7	*

Values show the results of individual measurements. * These values did not differ from the nickel concentration in the artificial saliva. EBVs were immersed and shaken (shaking frequency 100 times/min) in 3 ml of artificial saliva at 37° C for a period of 7 days. At 24-h intervals, 2 ml of the solution was extracted and 1:1 replaced with fresh solution. The nickel content of the extracted test solution was measured using the ELAN DRC-e ICP-MS with a cross-flow nebulizer. EBV, endobronchial valve.

(BAL), an infectious cause for the patient's deterioration was excluded, since there was no evidence of (myco)bacterial, fungal, or viral pathogens. HP was suspected, since there was marked BAL lymphocytosis (57% lymphocytes) with a CD4/CD8 coefficient of 2.6, and slight BAL eosinophilia (6% eosinophils). There was no increase of BAL neutrophils (2%). However, no IgE-mediated sensitizations to common inhalant allergens or molds could be detected (Sx1 and Rx2), and the total IgE was in the normal range (99 kU/L). There was no evidence of an inhalational antigen in the patient's history, since he denied exposure to an air humidifier, animals, or mold. Extensive patch testing could only reveal a strong skin reaction to nickel, but was negative for other possible antigens. Notably, EBVs with and without the silicone jacket (i.e., the nitinol frame only) did not provoke any skin reaction. Assuming a pulmonary and systemic hypersensitivity reaction to nickel, oral prednisolone (50 mg/day) was restarted, and the symptoms improved gradually. DLCO exceeded the baseline values over the following months (Table 1). Prednisolone could thus be tapered slowly, with no recurrence of the symptoms.

In vitro Evaluation

Compared to days 3–7 and to blank artificial saliva, there was a significantly increased nickel content in the extracted test solution after 24 and 48 h, respectively (Table 2).

The SEM images of EBVs before and after immersion in the artificial saliva are displayed in Figure 3. In the new EBVs, there was evidence of an incomplete silicone layer which had an imbricate surface (Fig. 3a). In the explanted EBVs, the silicone-free areas were larger than in the new EBVs (Fig. 3c) and the imbricate surface was only mar-

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ginally visible. Silicone-free areas were larger after abrasion and immersion in artificial saliva (Fig. 3b). Moreover, there was evidence of delamination of the silicone layer from the nitinol wire (Fig. 3d).

Discussion

Systemic hypersensitivity syndromes due to surgical implants are well known [10–12]. However, this is the first report describing HP after BLVR with EBVs in a patient with a proven contact allergy to nickel. For different reasons, this case is highly informative, and raises important questions regarding the clinical relevance of nitinol devices in patients with nickel allergy. Above all, nickel contact allergy occurs in up to 19% of the population and is the most frequent cause of allergic contact dermatitis [13].

Due to its physical properties, nitinol is an ideal metal alloy for various implantable devices [5]. However, different types of hypersensitivity reactions including severe bronchospasm after nitinol device implantation have been reported [14–19]. The systemic reaction to nickel was described 25 years ago as Kounis syndrome, i.e., concurrent chest discomfort, dyspnea, faintness, nausea, vomiting, syncope, pruritus, urticaria, hypotension, diaphoresis, pallor, palpitations, and bradycardia, with conditions associated with mast cell activation including allergic, hypersensitive, anaphylactic, or anaphylactoid insult [20, 21]. Thus, there is considerable concern about the release of nickel after nitinol device implantation [7].

Using ICP-MS, Nayak et al. [22] recently demonstrated a statistically significant increase of 10.35 ppb in the nickel ion concentration in the saliva of 30 patients after orthodontic aligning of nitinol arch wires. Shabalovskaya et al. [23, 24] reported that nickel release from nitinol is 10- to 16-times greater than that from stainless steel during the first day of immersion in cell cultures, decreasing to the level of stainless steel by the third day of immersion. Therefore, attempts have been undertaken to prevent nickel release, e.g., a nanoplatinum coating or a silicone layer in nitinol devices [25]. In addition, for patients with a positive history to nickel allergy, patch testing is thought to be necessary prior to nitinol device implantation to rule out nickel contact allergy-related complications. However, in the study of Kim et al. [8], positive reactions to nickel in a patch test were not associated with adverse outcomes following closure of atrial septal defects with a nickel alloy-based device.

Interestingly, our patient showed a strong reaction in the nickel patch test, but not to the nitinol-containing EBV. We hypothesize, therefore, that there must be a release of nickel from the EBV when in contact with the bronchial mucosa, which could possibly result in a hypersensitivity reaction. It is also possible that the patch test with EBV was too short to release the critical amount of nickel molecules.

In line with the findings published by Nayak et al. [22], we found in vitro evidence of nickel release from EBVs after immersion in artificial saliva, i.e., imitating the bronchial environment. The question as to how nickel ions find their way through the silicone layer covering the EBVs is apparently answered by SEM images. In both the new and explanted EBVs, we found an incomplete silicone layer, enabling the nitinol wire to be in direct contact with the bronchial mucosa. The reasons for this incomplete silicone layer are unknown. A handling failure during SEM seems unlikely, since the findings were confirmed by an independent laboratory. The SEM images showed that the assembly process of the valves on the SEM microscope was likely not responsible for the silicone-free zones of the valves. A second unanswered question is why the used valves showed a similar nickel release to that of the new ones, even though this was only detectable during the first 48 h. The explanted valves should have ended their nickel release during the first 48 h after their initial implantation, which had been performed months before explantation.

The concentration of released nickel exceeded the toxic limit of 20 μg/kg per day in only 1 measurement. However, this toxicity reference value is based on postimplantation loss/perinatal mortality derived from animal studies in rats [26]. In patients with nickel contact allergy, the release of nickel is of concern as it may lead to a hypersensitivity reaction. A particular toxicity reference value of 4 μg/kg for nickel-sensitized patients was thus proposed, based on the study of single exposures in humans [26].

According to our investigations, the nickel release was measurable solely during the first 48 h after the immersion in artificial saliva. This could be the reason that the hypersensitivity reaction in our patient was temporary, even though the EBVs were not removed and the corticosteroids could be tapered without the recurrence of symptoms. Additionally, there could have been a tolerance effect over time. However, likely following a different pathophysiological pathway, pneumonitis has been reported after exposure to nickel fumes [27].

Our study has a major limitation, which is due to the case report of only 1 subject and the small sample of EBVs investigated. It also remains unknown whether our ex-

perimental set-up is comparable to in vivo conditions, so we cannot say if the damage to the silicone layer or the release of nickel was possibly due to the experimental set-up. Furthermore, it remains unproven that the reported HP was actually due to nickel hyperreactivity. Admittedly, we did not perform a rigorous blood test of common HP triggers, since the patient denied having had any corresponding exposures. Nevertheless, the findings are unique and relevant for the understanding of the biological behavior of nitinol in contact with human tissue.

Conclusions

Although this is only the first case of HP after EBV treatment and no causative relationship was confirmed, our finding of an in vitro release of nickel ions may contribute to the current knowledge on hypersensitivity reactions after nitinol implants in patients with nickel contact allergy. The growing number of reported hypersensitivity reactions to nitinol, with its widespread applications in various medical implants including airway stents and valves, justifies further in vitro and in vivo studies to confirm our findings.

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Statement of Ethics

The testing of EBVs was waived by the local Committee of Ethics with a certificate of non-objection, since neither patient information nor biological materials were investigated. The patient gave permission for publication of his medical data.

Disclosure Statement

D.F. is an honorary speaker and L.F. is a shareholder for PulmonX International Sàrl, Neuchâtel, Switzerland. All authors have no conflicts of interest in conjunction with this study.

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